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Structural and Functional Brain Changes in Emotional Disorders: Foundations of Neurocirculatory and Neurotrophic Hypothesis of Depression

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ABSTRACT

Depression is one of the most common mental illnesses encountered by clinicians of all kinds. This is the case with major depressive disorder (MDD). According to the WHO, its relative lifetime prevalence is 16.2% and the annual prevalence is 6.6%.

Introduction. A diagnosis of MDD according to DSM-IV criteria, referred to as major depressive disorder (MDD), requires at least 5 symptoms to be present for at least 2 weeks if major depressive episodes (MDE) develop: low mood, feelings of worthlessness/guilt, thoughts of death or suicide, loss of interest in others, appetite disturbance, sleep disturbance, psychomotor changes, hypo or anger, concentration problems, and indecision. Although MDD is often described as an episodic illness, recent prospective studies have shown that it has a more recurrent course. For example, a 15-year study of 380 patients found that 73% of patients with BDE had a recurrent course. Moreover, the development of each BDE increased the risk of developing a subsequent one. Similar results were obtained in the international STARD (Sequenced Treatment Alternatives to Relieve Depression) project, which followed 1500 patients with BDD, of whom 74% had more than one BDE.

The recurrent course of MDD is thought to be triggered by the development of a series of neurobiological abnormalities that increase the body's vulnerability to the development of new MDD. Accordingly, the kindling hypothesis has been proposed, in which each BDE becomes a trigger for a new depressive episode, a phenomenon that intensifies over time. As the number of BDEs increases, their subsequent development becomes increasingly related to the previous number, rather than to stressors in the patient's life.

Accordingly, the kindling hypothesis has been proposed, in which each BDE becomes a trigger for a new depressive episode, a phenomenon that intensifies over time. As the number of BDEs increases, their onset becomes increasingly related to the prior number, rather than to stressors in the patient's life. S. Monroe and K. Harkness attribute the swaying of the illness to a reduction in

the threshold of defence (stress sensitisation) as the number of depressive episodes increases, and/or an increase in the spontaneous dysregulation of the neurobiological systems responsible for the development of MDD. K. Kendler et al. in a risk analysis of recurrent seizures in a twin cohort, showed a major contribution of genetics to the development of 'rocking' phenomenon. This study also found a reduced association between stressors and onset of recurrent MDD in patients at high genetic risk.

Risk factors for recurrent MDD also include family history of depression, early separation of the child from the mother (deprivation), and inadequate treatment in the initial stages of the disease. Some researchers have suggested that any life events from birth to presentation increase the risk of repeated attacks of MDD.

The chronicity of the MDD course suggests the presence of slowly increasing neurobiological sequelae, leading to a "rocking" disease. This makes a practical recovery in MDD patients increasingly unlikely, particularly in the later stages of the disease. While patients with disease duration less than 1 year have a 16% chance of recovery, patients with MDD of more than 5 years have less than 1%. The longer the interval between previous and subsequent MDDs, the greater the likelihood of recovery. If it exceeds 1 year in the early stages of the disease, the likelihood of non-resumption of a new episode is as high as 20% .The recurrence and chronicity of MDD reduces the prospect of treatment, with the aim of prolonging the periods between attacks rather than reducing or completely eliminating all major symptoms.Functional and structural changes in the brain in MDD.There are a number of neurobiological abnormalities associated with MDD. These are particularly prominent in limbic structures and their connections to affect regulation. These neuroanatomical areas include the medial, orbitofrontal and dorsolateral areas of the prefrontal cortex, the anterior cingulate cortex, and the ventral striatum, which includes the adjoining nucleus, amygdala and hippocampus. It is suggested that abnormalities found in these structures in MDD patients form the basis for its formation.

As an integrative circuit, the prefrontal cortex, cingulate cortex, amygdala and hippocampus provide not only mood regulation but also learning ability and contextual memory. In addition, the corresponding areas of the prefrontal cortex are relevant to pain, aggression, sexual functioning and eating behaviour, the development of affective disorders, and the support of executive functions, attention and working memory. Individual parts within the anterior cingulate cortex have different functions: the dorsal part of the anterior cingulate cortex provides some cognitive and executive functions, the ventral part of the anterior cingulate cortex processes emotional and motivational information; the anterior cingulate cortex monitors behaviour and cognitive functions.

Hyperactivation of the ventromedial and orbitofrontal prefrontal cortices, as well as decreased activity of the dorsolateral prefrontal cortex, has been found in patients with MDD. Based on the function of these brain regions, it has been suggested that these abnormalities are responsible for the symptom manifestation associated with MDD. Hyperactivity in the ventromedial, prefrontal cortex is associated with increased sensitivity to pain, increased anxiety, depressive rumination and tension. Hypoactivity of the dorsolateral prefrontal cortex can cause psychomotor retardation, apathy, attention deficits and working memory. Magnetic resonance imaging (MRI) has revealed a decrease in 'communicability' between the amygdala and anterior cingulate cortex. Due to the loss of these connections, the anterior cingulate cortex loses its inhibitory ability to be an emotional regulator, leading to the development of a motivational and affective gap .

Being at the intersection of limbic, cognitive, executive and neuroendocrine regulatory pathways, including the hypothalamic-pituitary-adrenal axis, the hippocampus must be particularly vulnerable in MDD. P. Videbech and B. Ravnkilde, who summarised 12 studies using meta-analysis, found that hippocampal volume is significantly reduced in MDD compared

to normal, and this reduction is observed bilaterally with a slight predominance on the right side. A number of other studies have shown that the decrease in hippocampal volume is directly proportional to the number of BDEs and the duration of BDD. Even in the remission period after BDE, patients continue to experience a slow decline in already reduced hippocampal volume .

The difference in hippocampal volume between MDD patients and controls is not always due to the disease alone. Studies have shown a genetic contribution of 54% to reduced hippocampal volume. Studies of autopsy brain tissue of MDD patients have shown a reduction in hippocampal size due to increased neuronal density and reduced neuropil volume (due to reduced dendrite branching).

The combined results of genetic, neuroanatomical, and clinical studies suggest that reduced hippocampal size is a predisposing factor for the occurrence of MDD. Treatment fails to normalise hippocampal volume, resulting in the patient's inability to recover fully.

Molecular processes mediating neurobiological changes in MDD

Disturbances in the hippocampus through a feedback mechanism can lead to dysregulation of the function of the structures concerned. High levels of the major stress hormone cortisol, which affects neuroplasticity and cellular resistance, play a major role. The disturbed balance between glucocorticoid and mineralocorticoid hormones, as well as the high density of glucocorticoid receptors (GR) in the brain in MDD leads to vulnerability of hippocampal neurons. As a consequence, hippocampal cell atrophy develops, leading to even greater neuroendocrine dysfunction and loss of controllability of hippocampal mediated brain systems. A consequence of increased levels of glucocorticoids (particularly cortisol) and decreased functional activity of the hippocampus is a decrease in GH sensitivity. Under chronic stress conditions (with elevated cortisol levels), a decrease in GH sensitivity can have negative consequences, as insufficient signalling through GH "turns off" the stress protection feedback mechanism. As a consequence, hypothalamic-pituitary-adrenal hyperactivation occurs, which, combined with activation of brain amygdala function, and increases the sympathetic tone, which in turn causes increased release of proinflammatory cytokines from macrophages. Increased secretion of proinflammatory cytokines (interleukins 1 and 6 and tumour necrosis factor TNF-α) reduces insulin levels and GH sensitivity, exacerbating metabolic and neuroendocrine disturbances. Clinically, these disorders are manifested by symptoms of fatigue, loss of appetite and libido, and hypersensitivity to pain.

Pro-inflammatory cytokines can also reduce neurotrophic cell support and monoamine neurotransmission, which in turn leads to neuronal apoptosis and impaired glia function and neuronal-glial relationships in MDD. The importance of these relationships is determined by the fact that glial cells are involved in complex interactions with neurons; maintain homeostasis of the neuron and its environment by regulating the content of electrolytes, neurotransmitters, cytokines and neurotrophic factors. Recently, much attention has been given not only to astro- but also to microglia, which is associated with immune dysregulation and additional production of pro-inflammatory cytokine release. Neurons, in turn, reciprocally support glia functioning through neurotrophin production. Brain-derived neurotrophic factor (BDNF) plays an integral role in the maintenance of norm**al neuron-glial interaction**. Being involved in neurogenesis, BDNF is the main neurotrophin in the hippocampus. As a dimeric protein involved in cellular maintenance, plasticity, growth and death (apoptosis), BDNF is structurally related to nerve growth factor and is wide**ly distributed in the brain**. BDNF, interacting with tyrosine kinase receptors, is responsible for cellular resistance to external factors and long-term potentiation effects. However, pro-BDBF, a BDNF precursor, binds to p75 receptor and may cause forced reduction of structures providing intercellular contacts, such as dendritic spines and cell death. Depending on the amount of BDNF expression, this process can be expressed to varying degrees. This process is regulated by various neurotransmitters (glutamate, gamma-aminobutyric

acid, serotonin, norepinephrine, acetylcholine, dopamine **and hormones)**. Preclinical and clinical studies show that BDNF dysregulation occurs in chronic stress and depression. In animal models of depression, a decrease in BDNF synthesis expression in **brain tissue has been shown** (similar results were obtained using models with acute or chronic pain stimulation of animals). Reduced serum BDNF levels have been found in untreated patients with BDNF compared to treated pa**tients or healthy controls.** Similar results were obtained from autopsy specimens from the brains of MDD patients (post-suicide): reduced levels of BDNF and neurotrophin type NT-3 compared to specimens from MDD patients **who didn't die by suicide).** The above data allowed the famous Venezuelan scientist Fuad Lechin to formulate the so-called neurocirculatory and neurotrophic hypo**thesis of MDD pathogenesis.** This hypothesis is based on the idea of the existence of links between systems of neurotransmitters or neurotrophic factors in the periphery (blood, cerebrospinal fluid, etc.) and systems relationships between these same neurotransmitters or neurotrophic factors in the CNS in depression (MDD) and other psychiatric disorders. As part of the development of this hypothesis, it has been shown that stress and genetic vulnerability through changes in the system of relationships between mediators, neurohumoral and neurotrophic factors in the periphery increase central glucocorticoid steroid production, which leads to impaired cellular plasticity and a decrease in the growth factor and GH s**ensitivity system.** The synthesis of neurotrophic growth factors such as BDNF (in blood and CNS) is also decreased. This causes negative structural and functional changes in the limbic system, especially the hippocampus. In chronic and recurrent forms of MDD, there is a gradual atrophy of the hippocampus, followed by dysregulation in th**e limbic system neurochips.** According to this hypothesis, recovery or remission of MDD depends on the reversibility of these processes, especially an increase in BDNF synthesis with treatment.

Within the neurocirculatory and neurotrophic hypothesis of MDD, the monoamine theories (serotonin, noradrenaline) become complementary. Recall that according to the monoamine theories, depression is associated with low levels of monoamine neurotransmitters, especially serotonin and noradrenaline. Recent MRI studies of patients with untreated depression have shown increased protein density of the enzyme monoamine oxidase A (MAO-A), which has non-specific enzymatic activity against both serotonin and norepinephrine. Therefore, the current version of the monoamine theory of depression postulates that a prolonged decrease in serotonin and noradrenaline levels due to MAO-A activation in different parts of the brain of patients leads to a disruption of serotonin and noradrenaline transporter proteins (SERT) and resulting in worsening depression. Serotonin and noradrenergic ascending nerve fibres emanate from brainstem nuclei and innervate the limbic system, prefrontal cortex, associated with structures involved in mood regulation; descending pathways pass through the dorsolateral spinal cord and are associated with regulation of pain sensitivity thresholds. Therefore, depending on the magnitude of changes in functional activity of SERT or norepinephrine transporter protein in the respective brain regions, the manifestation of different clinical manifestations of depression can be observed.

The role of neurotransmitters in the development of remission in MDD

A large number of studies have shown that treatment of MDD with selective serotonin reuptake blockers (SSRIs) or norepinephrine blockers (SNRIs) increases serotonin or norepinephrine levels in the brain of patients, respectively. Prolonged treatment with these drugs also increases levels of cyclic adenosine monophosphate (cAMP) in the brain, which stimulates a specific protein kinase A. Activation of this enzyme activates the part of the cell genome responsible for BDNF synthesis. Antidepressant-induced production of cAMP also increases GH sensitivity, inhibits the negative effect of increased cytokine production, and thereby restores their functional activity and regulation in the corresponding neural circuits.

The effect of increased levels of monoamines (dopamine, serotonin and norepinephrine) during antidepressant treatment, associated with increased synthesis of BDNF and other neurotrophic factors, is one of the leading in the mechanism of their antidepressant action. Animal studies have shown that increased levels of monoamines (serotonin and norepinephrine) with chronic administration of antidepressants causes increased levels of BDNF in brain astrocytes. It has been shown in clinical studies that serum BDNF levels normalise when patients with MDD are successfully treated with antidepressants. Serum levels of BDNF are thought to reflect its synthesis in the brain. This is supported by animal experiments and the fact that BDNF freely crosses the blood-brain barrier. It has been shown that the degree of improvement in patients treated with antidepressants with simultaneous inhibition of serotonin and norepinephrine reuptake (dual reuptake inhibitors) significantly correlates with an increase in serum BDNF levels. Studies of postmortem brain samples have shown that in the brain tissue of patients who died during treatment with dual reuptake inhibitors, higher levels of BDNF were detected than in brain samples taken from untreated patients .

A study noted that a positive response to antidepressant treatment was accompanied by normalization of cortical activity. After 1 week of treatment, patients had an increase in hippocampal activity and a decrease in posterior cingulate and prefrontal cortex activity. After 6 weeks of treatment, responders showed signs of normalisation of limbic system activity and increased prefrontal cortex activity, while responders showed no change after the first week. Normalisation of amygdala and anterior cingulate cortex functioning also appeared to be associated with a positive response to treatment. In addition, antidepressant-resistant MDD patients have been found to have elevated levels of proinflammatory cytokines compared to controls or euthymic MDD patients.

A study of the reduction of MDD symptoms in the course of treatment showed its relationship with regional changes in brain metabolism in patients. Thus, a decrease in the severity of cognitive impairment was correlated with an increase in the activity of the dorsal part of the anterior cingulate cortex, while a decrease in manifestations of fatigue syndrome and psychomotor retardation was associated with a decrease in the activity of the ventromedial zone of the prefrontal cortex. Interestingly, these correlations were observed regardless of psychopharmacological or psychotherapeutic treatment.

There is a view that the restoration of neurobiological regulation in MDD through increased synthesis of neurotrophic factors and, consequently, neurogenesis, is probably the common radical determining the effectiveness of treatment, whether it is psychopharmacological, psychotherapeutic or somatic (in the latter case, the use of diet and special physical exercises is meant).

The "rocking effect" and chronicity of MDD in its long-term course makes it important to find the most effective therapy already at the first attack of the disease. Long-term studies have shown that the best predictor of the course of the disease is the patient's response to treatment already at the first attack, i.e. within the first 6 weeks of the attack. This is of particular importance for elderly patients, in whom previous inadequate antidepressant treatment may lead to pharmacoresistance. A positive patient response to antidepressant treatment early in the course of illness provides a chance that further quality improvement in psychopharmacotherapy will lead to full or partial recovery.

The use of a broader spectrum of antidepressants, or an appropriate mix of drugs with different mechanisms of action, is considered one way to improve the quality of treatment of patients with MDD. At the same time, the results of a large meta-analysis, which included 92 studies (17,036 patients), showed similar effectiveness of serotonin- and noradrenergic antidepressants. However, a new generation of antidepressants that are dual selective reuptake inhibitors (both

serotonin and norepinephrine), dual antidepressants, have been shown to be more effective than SSRIs and SSRIs. Dual antidepressants were particularly effective when pain symptoms were present in the depression, which is known to be characteristic of masked depression. This is due to the synergistic activation of the serotonin and noradrenaline systems when treated with dual antidepressants.

The neurocirculatory and neurotrophic hypothesis of depression shows that the factors that initiate an episode of MDD and those that support the development of the illness are different. Initially, vulnerability to the effects of stress and genetic predisposition to the disease interact to initiate a cascade of neurobiological disorders that disrupt normal dynamic connections in brain areas involved in the regulation of mood, cognition, physical and mental activity, pain sensation, etc. With chronicity of the disease, further structural and functional abnormalities begin to potentiate as the course of MDD progresses.

The primary goal of treatment in the aftermath of chronic MDD is to restore normal functioning and prevent further structural and functional neurobiological abnormalities in the brain of patients. Increasing serotonin and noradrenergic neurotransmission with antidepressants initiates restoration of neurotrophic factor synthesis (especially BDNF), which normalizes glucocorticoid activity and neuroendocrine regulation. The use of dual antidepressants (serotonin and norepinephrine reuptake inhibitors) increases the likelihood of achieving remission through the complex reduction of emotional and somatic symptoms (including pain) in depression. According to the neurocirculatory and neurotrophic hypothesis, early treatment outcomes determine the prognosis and recurrence of MDD. The presence of residual symptoms during treatment also influences the further course of the disease. When remission is achieved, patients should be informed about the greater benefit of continuing long-term, continuous treatment rather than episodic or incomplete treatment. Treatment that includes individual or group cognitive therapy along with active psychopharmacotherapy promotes correction of molecular factors in disease pathogenesis, which reduces the subsequent risk of MDD exacerbation. **Conclusions**: When remission is achieved, maintaining normal brain metabolism is more important than preventing a developing exacerbation. This requires concerted action by the patient and physician in order to maintain a fully or partially normalised neurobiological homeostasis.

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